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(An Undergraduate Publication)

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EDITORIAL

THE FIRST DECADE.

With this number the University of Toronto Medical Journal marks the beginning of its tenth year of existence. One can imagine that the students of ten years ago, whose brain-child this Journal was, must have looked forward with some trepidation concerning the future of their project; there must have been those who hoped that it would live to pass through the most treacherous time of a child's existence—the first decade; but there must also have been those who feared for this new-born venture in journalism which would have to travel along an uncharted course. We, at this end of the decade, can only hope that the Journal, as it stands to-day, fulfils to some limited degree the aspirations of its founders, and that, having weathered the first ten years of life, can now look forward with the vision and enthusiasm of youth to a more brilliant future.

The University of Toronto Medical Journal has lead the way in the field of undergraduate medical journals on the continent. The past ten years has seen many of the leading medical centres follow Toronto in the publication of student journals. May we always prove a worthy leader!

At such a time it is natural for us to pause and to consider our position. Ten years of existence have proven that the journal is no longer an experiment, but that it plays a definite part in the undergraduate life of the Faculty of Medicine. One asks the question, "Of what value is the Journal to the Medical Student?" It has been shown that

it is valuable from three standpoints. First, the reader—from the Journal the reader can obtain authoritative information on all varieties of subjects, written especially for medical students. Second, the contributor—the opportunity is offered to all students to gain experience in assembling and composing articles, such experience is invaluable, when one considers the necessity of medical literature in modern medicine. Third, the staff—the opportunity is offered to all students to become acquainted with some of the intricacies of journalism.

PRESIDENT CODY.

It is with great pleasure that we welcome the new President of the University, the Hon. and Rev. H. J. Cody. Drk Cody comes to us as President after many years of association with educational work in Ontario. He has already shown himself to be keenly interested in all student activities, becoming actively associated in many student organizations. Dr. Cody has always been extremely interested in the Medical Profession, and we feel that, as President of the University, he will continue this interest by his association with the undergraduate medical students.

It was with extreme sorrow that we noted the sad passing of Mrs. Cody. May we express, on behalf of the medical undergraduate body, our sorrow to President Cody.

STAFF ADVISOR.

In the past few years it has been customary to have no one member of the Faculty to act as advisor to the Medical Journal. The Editorial Board is very pleased to announce that Dr. E. A. Linell has very kindly consented to act in this capacity. We feel that it is highly desirable to have a member of the Faculty, from whom we can seek advice, concerning policy, and who can help to provide a certain continuity to an enterprise which of necessity must possess an ever-changing staff. Dr. Linell has always shown great interest in student activities, and we feel confident that his advice and his contact with the Journal will prove most valuable.

ASSISTANT BUSINESS MANAGER.

The position of Assistant Business Manager of the Journal is vacant. Applications for this position will be received by the Editor at Room 107, Anatomy Building. The occupant of this position will become Business Manager, if his services prove satisfactory. It is advisable that the applicants be in the lower years, not above third, and preferably that they have had some general business training.

The Examination of Dermatological Cases.

By N. M. WRONG, M.B.

A plan of history taking and examination is essential to the diagnosis of cutaneous disease. By following a definite method, more information can be gleaned in a shorter space of time and there is less likelihood of missing important data.

At the first examination, it is essential that the patient be suitably exposed so that the lesion or lesions may be seen as a whole, a general impression formed of the patient's degree of physical fitness, and any obvious abnormalities noted.

It is not intended in this article to discuss general examination of the patient. Of course, this is necessary in all cases except where the lesions are obviously concerned with the skin alone. In diseases associated with pigmentation of the skin, one must keep in mind pathological conditions of the suprarenal, thyroid, alimentary tract (as in acanthosis nigricans); in various erythematous and papular eruptions, one must keep in mind the acute exanthemata ,syphilitic and tuberculosis infections; and in purpuric eruptions, it is essential to search for an underlying cause.

The points to be elucidated in taking a history from a dermatological patient will next be dealt with very briefly:

1. *Age.* This is of some importance in differential diagnosis, most notably in malignant neoplasms and in tinea of the scalp.

2. *Sex.* A few skin diseases have a definite sex incidence. Lupus erythematosus is more common in females; whereas, occupational affections of the skin are, of necessity, more common in males.

3. *Race.* Lupus vulgaris is extremely rare among native-born Canadians and favus (a destructive type of ringworm infection) is most common among Central Europeans.

4. *Clothes.* Dyed articles—furs in the case of females; hat bands in the case of males—are the chief offenders.

5. *Cosmetics.* Many of these cause an eruption only after a considerable period of application.

6. *Recreations.* This may seem unimportant but, occasionally, it gives the clue to the cause of a Dermatitis Venenata. In this disease, one may find that the handling of plants or flowers as a hobby may be the cause of the dermatitis.

7. *Occupation.* If the patient is an industrial worker, this must be inquired into thoroughly and the actual substances, which are handled, ascertained. The same is true of women doing housework. Here, the kinds and amounts of cleaning solutions and polishes, which are used, must be learned.

8. *Medicated Applications.* The original eruption may have been altered completely by application of irritating ointments or lotions.

9. *Ingestion of Drugs.* The reader is referred to any standard text-book for a list of drugs and the lesions which they may produce. It is sufficient to say that drug eruptions are very numerous and varied.

10. *Exposure to Infection.* This is of particular importance in the case of venereal disease, the acute exanthemata and ringworm infections.

11. *Recent Disease of the Nose and Throat.* This is of importance in the Acute exanthemata, syphilis, erythema multiforme and erythema nodusum.

12. *Exudative Diathesis.* The presence of eczema, asthma, or hay fever in the patient or in immediate relatives, is of prime importance in the allergic

diseases, e.g., eczema, prurigo, urticaria, etc.

13. *Mental State.* An attempt should be made to gauge the patient's reaction to his eruption, which may be out of all proportion to the severity of the latter.

Examination of the Skin As a Whole.

1. Color of skin and mucous membranes.

Under this heading one should consider pallor, yellowing, bronzing, patchy or generalized pigmentation or loss of pigmentation

2. The state of the skin.

Any excess or diminution in the amount of moisture and oil on the skin shoull be searched for.

3. Pliability.

One should determine if the skin is normally elastic and supple, or whether there is localized or generalized hardness, thickness and loss of elasticity.

4. Oedema.

It should be determined whether or not there are localized or generalized areas of oedema and if this oedema is dependent or non-dependent.

5. Texture.

There is a wide variation in this from the fine clear skin of the blonde to the thicker, coarser skin of the negro, but any variation from this wide norml should be determined.

It will now be attempted to outline briefly the examination of the mucosa and skin, the latter being arbitrarily divided into areas to facilitate description. The lesions, which may be encountered in these areas, will be discussed concisely and the various diseases, which may cause these lesions, will not be enumerated, as it is felt that it would be quite beyond the scope of this paper to enter into a discussion of differential diagnosis, involving all the skin and easily accessible mucous membrances. It should be pointed out at this juncture that the diagnosis of skin diseases depends upon the recognition of the primary lesion. Areas which have been excoriated by scratching, altered by treatment or are undergoing a spontaneous involution are, therefore, not as important from a diagnostic standpoint as fresh, unaltered areas.

The Scalp.

In the examination of the scalp, first attempt to gain a general impression of hair growth and then of abnormal oiliness, dryness and scaliness. One should then search for localized areas of baldness. If found, they should be examined, with the following considerations clearly in mind:

a. Surface—scaling or smooth.
b. Hair loss—practically complete or only partial loss in the area.
c. Presence or absence of short broken off hairs.
d. Presence or absence of exclamation mark hairs, that is, hairs pigmented and normal in size at the distal end but pale and atrophic at the proximal end.
e. Redness, atrophy or scarring of the scalp at the site of baldness.

Having gained an idea of general hair growth and of generalized or localized areas of alopecia, examine the scalp for the presence of scaling, which may be diffuse or localized. If scales are found one should note their color, ease of detachment, character of the base when they are detached, i.e., reddened or pale, dry or moist, granulomatous or smooth. Then the scalp should be searched for crusts, which should be examined for color, superficiality and character of base when detached. Crusting in the scalp is caused most usually by pediculi, and the hair should be searched carefully for pediculi and their ova. There are numerous other abnormal conditions found in the scalp, but this outline includes the commoner ones.

Face, Neck and Ears.

In these situations, the first impression gained would be that of color, whether normal, or localized, or diffuse areas abnormally pale, red or blue. Then, localized patches of inflammation should be searched for with a view to position, symmetry, size, shape, surface, induration and association with scaling, ulceration, scarring or lichenification. Scaling areas should be examined as regards position, size, symmetry, color and adherence of scales, margins, thickness, character of base when scale removed, and, finally, as regards association with redness, follicular plugging, ulceration or scarring. Then one should take note of any abnormal oiliness or dryness of the skin and at the same time see if there are any comedones.

Then examination of any papules present should be made from the standpoint of position, size, association with hari follicules, color, surface (scaly or smooth, flat or acuminate) borders (round or quadrilateral), and of induration. Any vesicles or bullae present should be examined with a view to size, tension, depth in the skin, surrounding zone of inflammation, and to association with ulcers, crusts or pustules. The latter should be examined keeping the above points, relating to vesicles and bullae, in mind. One should examine areas of ulceration for position, size, shape, borders (regular or serpiginous, raised or flat) bases (clean or covered with membrane) and for induration. If wheals are present, one should note their size, position, surrounding zone of inflammation, presence or absence of central puncture, and association with oedema in areas where the subcutaneous tissue is lax. Finally, scarred areas, which may be present, should be examined with a view to color, elevation above surface, attachment to deeper structures, and association with ulceration or pigmentation.

Trunk, Genitals, Axillae and Perineum.

In these localities the same routine examination should be followed; in the hairy areas, axillae, pubes and perineum, as outlined for the scalp and on the glabrous skin as was outlined for face and neck. The genitals present lesions which are uncommon elsewhere on the body. Ulcers should be regarded as specific in origin until proved otherwise. Pruritus vulvae may be due to irritating vaginal discharges, or to glycosuria. There is also a form of pruritus which may affect one or more of scrotum (vulva) and anus which is accompanied by no visible skin change. Pruritus ani alone is often associated with haemorrhoids.

Upper and Lower Extremities.

The arms, forearms, thighs and legs present lesions which are almost analogous to those found elsewhere on the body, and the same routine examination should be followed. On the other hand, the wrists, ankles, palms, soles and interdigital spaces present lesions which are not found elsewhere. These latter areas should first be examined as outlined above, and then the following additional lesions should be searched for. On the anterior surfaces of the wrists, the ulnar borders of the hands, the palms and soles, and in the interdigital spaces may be seen dark wavy lines, two to four millimetres in length, situated in the epidermis and often associated with vesicles or pustules. These are scabetic burrows, and are pathognomonic of the disease. The palms and soles may present localized or generalized, unilateral or bilateral thickenings of the horny layer of the epidermis, which are known as hyperkeratoses, and are much more marked in these localities, although they do appear on other parts of the body.

Mucous Membranes—Oral and Vulvar.

First the color, and then any areas of pigmentation of mucosa, should be noted. Following this, there should be a systematic examination for localized

areas of inflammation, for papules, for vesicles or bullae, for pustules, for areas of ulceration, in which the character and ease of detachment of any attached membrane should be carefully noted, for scarring and for the presence of nodules deep in the corium or in the subcutaneous tissues. Finally, fissuring at the mucocutaneous junction or on the tongue and areas of hyperkeratosis should be carefully examined.

Lymphatic Glands.

In all cases, a thorough examination of the superficial lymphatic glands should be made. It is not within the scope of this paper to discuss the differential diagnosis of glandular enlargements.

Aids in Diagnosis.

1. A pocket lens is invaluable for the study of the finer structure of skin lesions.

2. Microscopical examination of hairs, or scales, suspected of being infected with fungus, should always be done after mounting them in a 10% aqueous solution of Potassium Hydrate. Biopsy sections should be taken whenever indicated. Identification of organisms by direct smear and cultural methods and of fungi by the latter method should be attempted whenever feasible.

3. An ultra-violet light, fitted with a Wood's Glass, is of value in the diagnosis of ringworm of the scalp, as hairs, infected with the Microsporon Audouinii, fluoresce under this light.

4. The application to the skin, for a period of twenty-four hours, of substances, suspected of being the cause of dermatitis, is often a valuable aid in diagnosis. This test is known as the patch test.

5. The Prausnitz-Kustner test is sometimes employed for the same reason as the patch test. For the technique of these two tests reference may be had to any recent textbook.

6. Serological Test — Wasserman, Kahn, etc., may often prove of great value in clinching the diagnosis.

Summary.

1. A short, comprehensive history should first be obtained, embracing age, sex, race, occupation, recreation, clothing, cosmetics, medicated applications, drug ingestion, exposure to infection, recent disease of nose and throat, allergic and mental disease.

2. A general examination should then be made of the patient.

3. The skin and mucous membranes should be examined systematically and the various abnormalities, in the different areas, noted.

4. Laboratory examination should then be done, including bacteriological, pathological and serological methods.

Conclusion.

If the reader will but take a reasonably careful history and then examine systematically all parts of the skin and mucous membranes, and supplement this by any necessary laboratory work, it is felt that the great majority of the commoner skin diseases will be easily recognized.

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See editorial. Room 107, Anat. Bldg.

Symptom Complexes of Thrombosis and Embolism in Relation to the Arterial Blood Supply of the Central Nervous System.*

By W. J. HENDRY, B.A., '33.

Of the systems designed for the co-ordination and control of the vital phenomena taking place in the body, the most delicate is the central nervous system. It is our purpose in this paper to consider the effects produced by vascular lesions, more particularly embolism and thrombosis, in various portions of the central nervous system. Too commonly it is believed that the only symptoms of "stroke" are a spastic hemiplegia, either permanent or transitory, possibly with aphasia (either motor or visual) or hemianopia. While in a majority of cases these may be the prominent symptoms, there are other symptom complexes which should not be overlooked. To understand these we must review the anatomy of the blood supply to the brain.

Let us first consider a few general features of the cerebral circulation. The blood supply is from four arteries —the two vertebrals and the two internal carotids. The vertebral artery is a branch of the first part of the subclavian artery. At the base of the brain these different arteries are so connected directly or indirectly by that remarkable anastomosis, the Circle of Willis, that there is practically a common source from which large branches lying in the subarachnoid space are given off to supply the several parts of the brain.

In the pia meter covering the brain the different arteries again become connected with each other in a superficial freely anastomosing plexus. The internal branches of the plexus so formed are arranged in two groups, a central or ganglionic group, and a cortical group. From the cortical anastomosis arise branches which enter directly into the nervous substance both from the summits of the gyri and the walls of the sulci. These are short, medium and long branches passing at right angles into the gyri. The short vessels supply the gray matter, the medium, the more superficial white matter, and the long vessels penetrate to the centre of the white matter. The arterial capillary system arising from the penetrating twigs passes over into venous capillaries which converge to form corresponding venous twigs. These, in their turn, pass to the surface and join in forming a peripheral anastomosing venous plexus superimposed upon the similar arterial plexus.

From this venous plexus arise the different veins of the brain, which may or may not (more usually not) accompany the arteries for a distance. The veins eventually empty into the sinuses in the cranial dura mater. These sinuses, likewise confluent, drain to the commencement of the internal jugular veins.

The choroid plexuses of the ventricles of the brain are modifications of the general anastomosing peripheral plexuses. Branches of the choroid artery, a small but constant separate branch of the internal carotid artery, are the main source of supply to the choroid plexnses of the lateral and third ventricles. As these do not play any part in the localising symptoms of vascular lesions, we may dismiss them with this brief reference.

Let us now trace the course of certain of the most important arteries. The vertebral artery emerges from the foramen in the transverse process of the atlas, winds around the articular process of that bone and enters the skull through the foramen magnum. A meningeal branch, posterior and ante-

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* A paper delivered before the Alpha of Ontario Chapter of Alpha Omega Alpha, March 7, 1931.

rior spinal branches, and the posterior inferior cerebellar arteries, as well as twigs to the medulla, are given off before the two vertebral arteries unite at the lower border of the pons to form the basilar artery. This vessel runs upwards and forwards to end at the upper border of the pons by dividing into the two posterior cerebral arteries. The branches of the basilar artery include pontine twigs, the internal auditory artery which enters the internal acoustic meatis, and the anterior inferior cerebellar artery. This arises near the origin of the basilar and passes outwards across the pons, over the crus of the cerebellum to the front part of the under surface of the cerebellum. The superior cerebellar is another branch of the basilar artery, arising directly behind its bifurcation into the posterior cerebral arteries. It passes outwards and backwards over the pons in a course roughly parallel to the posterior cerebral artery, separated from it by the oculomotor nerve. Soon it winds round the cerebral peduncle close to and below the trochlear nerve to gain the superior surface of the cerebellum. Branches are given off to the pons, pineal body, choroid plexus of the third ventricle, and the cerebellum.

The cerebellum is supplied by three arteries on either side. These vessels form an extensive plexus in the pia-mater with extensions down into the sulci and fissures. From this anastomosis penetrating vessels pass into the substance of the cerebellar hemispheres. In addition, each dentate nucleus received a special vessel from the superior cerebellar or the anterior inferior cerebellar artery of that side. The veins of the cerebellum do not accompany the arteries. They spring from a superficial plexus to which the deep veins drain, and form three groups of veins on each surface, central and two lateral sets. These veins drain to the vein of Galen, and the transverse and the superior and inferior petrosal sinuses.

With regard to the medulla, much might be said of its blood supply. This has been carefully worked out by injection techniques, and is exceedingly important by reason of the relationships to the vital centres concentrated in this portion of the brain stem. Four arteries on each side supply the medulla the anterior spinal, twigs from the trunk of the vertebral, the posterior inferior cerebellar and the posterior spinal. The most lateral portion of the "open medulla" — the restiform body, which, it will be recalled, is the inferior cerebellar peduncle, is supplied by the posterior spinal artery. The portion between the restiform body and the olive is supplied by the posterior inferior cerebellar artery. The olivary nucleus and the nuclei of the ninth, tenth and eleventh nerves, derive their blood from the direct branches of the vertebral artery. Finally, the anterior spinal artery supplies the most mesial region of the medulla, including the pyramid (descending cerebro-spinal tracks), the mesial lemniscus (the ascending spino-thalmic tract), and the mesial longitudinal fasciculus — an intracerebral association tract.

The pons receives its blood supply from the ventral surface, from the basilar artery mainly, but to some extent also from the anterior inferior cerebellar and superior cerebellar arteries. The pontine vessels are of two main divisions — mesial and lateral. The mesial vessels supplying the central portion spring from the dorsal aspect of the basilar artery directly, to terminate in the nuclei in the floor of the fourth ventricle. The lateral vessels arising from off-shoots of the basilar artery are of two types. There are the radicular arteries passing into the pons in company with the roots of the fifth, sixth, seventh and eighth nerves, and the intermediate arteries which enter the lower surface of the pons rather irregularly. The veins from this region form a plexus in the pia-mater whence drainage is to the basilar veins, cerebellar veins and the inferior petrosal sinuses.

The posterior cerebral artery is frequently double. It passes lateralwards, receives the posterior communicating artery from the internal carotid, and winds around the cerebral peduncle to gain the tentorial surface of the cerebrum, where it lies just medial to the hippocampal gyrus. It then passes into the calcarine fissure, where it divides into its two terminal branches — the calcarine and the parieto-occipital arteries. It gives origin to the postero-medial and poster-lateral sets of central branches, the posterior chorioidal artery and cortical branches, which supply all the basal surface of the temporal and occipital lobes (except the temporal pole), the mesial surface of the occipital lobe and a strip extending half-an-inch in front of the patieto-occipital fissure. The lateral surface of the occipital lobe, along with a strip one-half to one inch wide along the lower border of the temporal lobe, is also supplied by this vessel.

Both the postero-mesial and postero-lateral sets of central arteries enter the brain substance through the posterior perforated spot. The former vessels supply the floor of the third ventricle, the posterior part of the thalamus and the hypothalamic region. The postero-lateral group supply the posterior portion of the internal capsule, the pulvinar of the thalamus, the corpora quadrigemina, the pineal body and the cerebral peduncles.

The internal carotid artery gives off the two other important cerebral arteries, the anterior and middle cerebral vessels. The anterior cerebral artery arises at the medial end of the Sylvian Fissure, passes forwards and inwards over the optic nerve to reach the great longitudinal fissure. Here the arteries of the two sides are joined by the anterior communicating artery. The anterior cerebral artery then gains the medial surface of the hemisphere by curving round the genu of the corpus callosum to supply the cortex of the whole of the medial surface of the frontal and parietal lobes to one-half inch in front of the parieto-occipital fissure. By some overlapping branches, the anterior cerebral artery supplies a strip on the supero-lateral surface of the hemisphere about an inch wide. On the basal surface this artery supplies the inner one-half of the orbital surface of the frontal lobe. It also gives rise to the antero-mesial set of central arteries which pass through the mesial portion of the anterior perforated space and supply the head of the caudate nucleus, the septum pellucidum, the columns of the fornix, genu of the corpus callosum, and the lamina terminalis.

The middle cerebral artery, the largest branch of the interal carotid, arises in the stem of the Sylvian fissure. It passes backwards on the surface of the insula, deep in the fissure, whence its branches emerge, and where it is accompanied by the vein of the lateral fissure. (Sylvian vein.) From the middle cerebral artery arises the antero-lateral set of central branches, and cortical branches are given off to supply the outer half of the orbital surface of the frontal lobe and all of the lateral surface of the frontal, parietal and temporal lobes except a strip one-half to one inch wide along the inferior border of the temporal lobe (supplied by the posterior cerebral artery), and a strip of the same width along the superomesial border of the frontal and parietal lobes which derives its blood from the anterior cerebral artery.

The anterolateral group of central arteries, too, enter through the anterior perforated spot, and may be divided into two sub-groups, of which the first are the lenticulo-optic or internal striate arteries, for it will be recalled that the region of the basal ganglia (the thalamus, caudate and lenticular muclei), is known as the corpus striatum from its peculiar striated appearance towards the anterior end of this region. The lenticulo-optic arteries pass through the segments of the globus pallidus and through the internal capsule, to both of which they give

branches, and terminate in the caudate nucleus and the thalamus.

The second sub-group of the antero-lateral group of central arteries consists of the lenticulo-striate or external striate arteries. These are larger and more numerous than the members of the lenticulo optic group. They pass upwards between the external capsule and the putamen into the internal capsule to terminate in the thalamus and in the caudate nucleus. On account of the larger size of the middle cerebral artery at its origin, and because it is the direct linear continuation of the internal carotid artery, emboli more frequently gain entrance to the middle cerebral artery than to any other cerebral vessel. One of the lenticulo-striate arteries which is longer and larger than the others, and which is a direct branch from the middle cerebral artery, has been named the "artery of cerebral haemorrhage," on account of the greater frequency with which it is ruptured or involved in vascular disease. The lenticulo-striate group of central arteries also supply the putamen, the external capsule and the claustrum.

The veins of the brain have been considered briefly in our discussion of regional arterial supply. They drain to the venous sinuses of the cranium which, for the purpose of our paper, need nothing more than our passing attention. These sinuses are sixteen in number — six unpaired median sinuses and five paired lateral sets.

In four positions there are communications between the venous sinuses and the veins outside the skull. These are by means of tiny emissary veins passing through foramina in the skull. The superior sagittal sinus is joined to the veins of the nasal cavity by a vein passing through the foramen caecum. The same sinus is also joined to the superficial temporal veins through the parietal foramina. The transverse sinus and the occipital or posterior auricular veins are united through the mastoid foramen, while the cavernous sinus communicates with the pterygoid plexus of veins by emissary veins passing through the foramen ovale or the foramen of Vesalius, or with the veins of the face via the ophthalmic vein.

The blood supply of the spinal cord now claims our attention. We have mentioned already the arteries of the cord. These are the anterior and posterior spinal arteries, both of which arise from the vertebral artery within the skull. The posterior spinal artery runs obliquely along the side of the medulla to the back of the cord, down which it passes behind the special nerve roots. It is reinforced at intervals by branches running inwards along the nerve roots, in the neck region, derived from the vertebral; in the thoracic from the intercostals, and in the lumbar region from the lumbar arteries. The posterior spinal artery can be traced as low as the end of the spinal cord.

The anterior spinal artery comes off the vertebral a little below its termination in the basilar artery. It descends obliquely inwards in front of the medulla, and at the level of the foramen magnum, unites with its fellow of the opposite side. The single vessel so formed, reinforced by a series of lateral branches as is the posterior spinal artery, passes down the anterior aspect of the cord beneath the pia-mater to the termination of the cord.

These vessels, along with their reinforcements, form a definite plexus in the pia-mater. Thence branches are given off to the substance of the spinal medulla. Generally speaking, the anterior spinal artery supplies a large wedge-shaped portion of the cord, with its base anterior. It supplies all the grey matter except the dorsal horn, the anterior column and the lower part of the lateral column of white matter. The posterior spinal arteries supply the dorsal horn of gray matter and the dorsal or posterior half of the lateral column of white matter.

The veins are arranged similarly to

the arteries. The central veins drain to a peripheral venous plexus, from whence arise six main longitudinal channels. The blood drains by intervertebral veins to the vertebral, intercostal and lumbar veins.

We are now ready to consider the questions of embolism and thrombosis. Of the three forms of vascular disturbance in the brain, thrombosis acts the most slowly as a rule; embolism produces the most sudden result, while haemorrhage is much the most acute lesion. The effects of haemorrhage may develop slowly, however. Embolism is the result of the lodging in the vessels of the brain of an embolus, which most frequently arises from the left side of the heart. Commonly, it is a portion of a vegetation from a fresh or from a recurrent endocarditis, or it may break off from a thrombus in the left auricular appendage, from a clot in an aneurysm, atheroma of the aorta, or from the region of the pulmonary veins. Globules of fat or bubbles of air may cause cerebral embolism. According to Osler, cerebral embolism is not infrequent in the puerperal condition. A majority of cases (89 per cent. according to Saveliew) occur in heart disease, though it is only rare cases that accompany the acute endocarditis of rheumatic fever. Recurring endocarditis attacking old sclerotic valves is a much more frequent precursor of cerebral complications. The embolus, as we have pointed out, arises most commonly in the left side of the heart, and so tends to reach the brain by the most direct route — the common, then the internal carotid arteries, passing most frequently into the largest and most direct branch of the last vessel— the middle cerebral artery, and, more usually, that of the left side. The vertebral artery and posterior cerebral vessels are much less frequently involved in the process. The cerebellar vessels, too, are less often affected, and embolism of the spinal cord is also an unusual occurrence.

Thrombosis may occur under four different sets of circumstances. Firstly, a thrombus may form about an embolus. Secondly, thrombosis may occur as a result of a lesion of the arterial wall — endarteritis, with or without atheroma, or more particularly in cases of syphilitic arteritis. Thirdly, the process may be seen in aneurysms, miliary or large; and, lastly, in such conditions as the anaemia of haemorrhage, chlorosis, septicemia, the cachexia of cancer, as a result of abnormal conditions of the blood. Foci of infection, such as infected teeth, are often seen in cases of cerebral thrombosis. Thrombosis occasionally follows ligation of the common carotid artery, and is most common in the middle cerebral and basilar vessels.

Let us turn now to the pathological changes occurring in the central nervous system. The embolus may retract or be carried further along in the blood

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stream to a smaller vessel. In either case there will be an improvement in the patient's condition. However, in the region about the embolus, oedema occurs, and thus cerebral oedema is the cause of coma so frequently seen in these cases. The chief result of embolism or of thrombosis is an infarction of the brain in the region supplied by the occluded vessel. The infarcted area may become infiltrated with blood —a haemorrhage infarction, or it may not — remaining pale — an anaemic infarct. The area infarcted becomes swollen, necrotic and infiltrated with serum. The nerve cells undergo degeneration, and that region of the brain which, it will be recalled, is rich in lipoid substances, becomes liquid in consistency. A portion of this fat is phagocyted by the microglia cells. However, except in the smallest areas of infarction, there is no filling in of the degenerated area by the connective tissue of the central nervous system — the glial cells. Thus, what in any other tissue in the body would result in scar formation, here results in the production of a cyst.

The question of whether the vessels of the brain are end arteries or not is a vexatious one. Cohnheim, in 1872, first enunciated the theory that infarcts could only occur in regions supplied by end arteries. Yet despite the open circulation in the spleen, infarcts are seen in that organ. Pfeifer, and later Cobb of Boston, have definitely shown that there are many well defined and clean cut anastomoses between the arterioles and in the capillary bed in the brain substance. The production of necrosis is explained by the fact that the ganglion cells of the brain are known to withstand even partial anoxemia badly. The relative lack of oxygen produced by the occlusion of one artery is sufficient, despite the collateral circulation, to cause necroses "in a tissue more dependent on its oxygen supply than any other tissue in the body."

Now, it should be clear to all that the position and extent of the softening depend upon the artery obstructed, and also to the point in its course where the obstruction occurs. Thus, if the middle cerebral artery be involved near its origin from the internal carotid artery, the anterolateral set of central arteries will be involved in addition to the cortical vessels, with the resultant softening of the corpus striatum, as well as of the cerebral cortex. However, once the embolus passes the origin of central branches, it usually lodges not in the main trunk, but in one of the branches of the middle cerebral artery; for example, in the branch to the supramarginal and angular gyri, or in the lowest branch to the superior convolutions of the temporal lobe.

Embolism and thrombosis may exist without symptoms, or may produce along with other symptoms a permanent or transient hemiplegia. Embolism is usually seen in a patient with heart trouble. It is sudden in its onset, causing no premonitory symptoms or possibly severe headache.

Thrombosis is gradual in onset. The patient may complain of headache, vertigo, or tingling of the fingers. Paralysis may begin in one part of the body, and gradually extend to involve one side, or the patient may notice embarrassment in his speech for several days, accompanied by loss of memory and incoherence of thought. Abrupt loss of consciousness is less common than in cases of embolism.

Let us now consider the symptoms resulting when the separate arteries are occluded.

The left vertebral artery is the one usually affected, and this rarely occurs alone. In this case, the nuclei of the medulla are involved, giving symptoms such as difficulty in swallowing or of phonation.

Occlusion of the basilar artery leads to lesions in the pons. Both motor paths may be affected, giving a double hemiplegia, or a crossed hemiplegia— the face is paralysed on one side, the arm and leg on the other—may be seen.

Dysarthria and dysphagia may be seen as well.

Should the posterior cerebral artery's main stem be involved, hemianopia and sensory aphasia will result. Occlusion of the main occipital branch leads to hemianopia. Should the posterior part of the internal capsule be involved, hemianaesthesia results. A lesion in the region of the corpora quadrigemina may lead to a paralysis of the third nerve on one side of the face, arm and leg on the other. Symmetrical thrombosis of both posterior cerebral vessels is possible, leading to an anopia and sensory aphasia.

Blockage of the internal carotid artery usually leads to hemiplegia, coma and death. However, occasionally evidences may be seen of infarction of the retina and blindness as a result of blockage of the opthalmic and central artery of the retina.

The middle cerebral artery is the vessel most commonly involved. A variety of symptoms result. If the occlusion is before the origin of the central arteries, permanent hemiplegia results. If beyond these, the paralysis may be transient, involving chiefly the arm and face. Should it be a left-sided lesion, aphasia results. Blockage of the branches to the inferior part of the left frontal lobe causes motor aphasia; of the branches to the supramarginal and left angular gyri, visual aphasia or alexia is produced, or there may be a right-sided hemianopsia. A lesion of the anterior and posterior central gyri causes total hemiplegia, while involvement of the left temporal gyri may lead to word deafness.

The anterior cerebral artery may be blocked and yet no symptoms occur, for the middle cerebral artery may provide sufficient collateral circulation. On the other hand, there may be produced a monoplegia of the leg or dullness of intellect.

Occlusion of the upper branch of the anterior spinal artery has led to paresis or paralysis of the muscles of the tongue, trunk or limbs, as a result of a lesion in the central part of the medulla.

With a case of thrombosis of the superior cerebellar artery, there was seen loss of pain and thermal sense on the homolateral side, and ataxia, atonia and asthenia on the heterolateral side. These symptoms were the result of involvement of the brachium conjunctivium and of the spinothalamic tract.

Quite a number of cases of occlusion of the posterior inferior cerebellar artery have been reported in the literature. The syndrome usually develops suddenly without loss of consciousness. The first symptoms may be dizziness and vertigo, often associated with nausea and vomiting, these last resulting from irritation of vagal nuclei. There is weakness in the arm and leg of one side, and when walking there is a tendency to fall, or to walk to one side. These, with the dizziness and vertigo,

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are the results of involvement of the vestibular nucleus in the medulla. Very often the patient has difficulty in swallowing, and, in some cases, an aphonia or weak and husky voice. These are the result of involvement of the nucleus ambiguus, the voluntary motor nucleus of the vagus nerve.

Horner's Syndrome (1) a ptosis of the upper eyelid, (2) miosis, (3) enophthalmos, (4) redness and flushing of one side of the face, a lessening or absence of perspiration on that side of the face, and (5) a relaxation and weakness of the muscles on one side of the face, is often seen in these cases —either in its complete form or portions of it by themselves. Various explanations are given; possibly it is due to a paralysis of the sympathetic centre and pathway on the same side.

Pain in the eye, back of the eye, or in one side of the face, may be a symptom, from involvement of the spinal coat of the fifth nerve. Or, again, less commonly, diplopia and nystagmus may be noticed, again due to the lesion involving the vestibular nucleus.

Thus, although thrombosis and embolism are most commonly recognized in the middle cerebral artery, we hope we have shown in our discussion the wider field which exists in the localization of vascular lesions in the brain.

The author wishes to express his thanks to Dr. G. W. Howland for his constructive criticism during the preparation of this paper.

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Phosphate Metabolism (Continued).

PART II.

By H. D. JENNER, B.A., '33.

Diseases Affecting Phosphate Metabolism.

It is proposed to deal here with disorders of phosphate metabolism, including those with only local, as well as those with general manifestations. Rather arbitrarily, they have been divided into four main groups, not as a classification, but merely for convenience in description.

(a) DISEASES DUE TO DIETARY AND ENVIRONMENTAL DEFECTS:—

(1) Infantile Rickets:—Concerning this condition, Hess states: "It is impossible to gauge its incidence accurately, but it seems safe to estimate that during the first two years of life, one quarter to one half of breast-fed infants, and approximately 75 per cent.

of bottle-fed infants develop rickets to some degree." The condition is less common in Canada and the U.S.A. than in most other parts of the world. In America it is found especially among negro children. Regarding seasonal incidence, the condition occurs with much greater frequency during late winter and early spring. The child is irritable with restlessness during the night and sweats profusely, especially about the head.

Infantile rickets in most cases is accompanied by a low inorganic phosphate concentration in the plasma. The normal infant's plasma contains 4 to 5 Mg. of phosphorus in inorganic combination per 100 cc. In rachitic plasma this is usually below 3 Mg. per 100 cc. This type is spoken of as low phosphorus rickets as contrasted with the less common form due to low serum calcium. Low calcium rickets is frequently associated with tetany. As a rule, the primary cause of rickets is not dietaries deficient in calcium or phosphorus, since it can occur on a milk diet containing adequate amounts of both these mineral constituents. Vitamin D is specific both for prevention and cure of rickets, and lack of this factor results in the rachitic condition. Certain cereals, notably oatmeal, are said to have a specific rachitogenic effect and to increase the tendency to develop rickets in absence of Vitamin D.

The pathological changes occurring include a general softening of the bones, allowing bending to occur on strain, a flaring out of the shafts of the long bones near the epiphysial lines, and a marked widening of the cartilaginous zone between shaft and epiphysis as seen in the X-ray picture. Low calcium rickets is more frequently associated with osteoporosis and liability to fracture. The mineral content of the bones is diminished below the normal figure. The phosphatase content of the plasma is higher than normal. The immediate cause of defective calcification lies in the plasma; rachitic bone, when placed in normal plasma, shows calcification in vitro, but when placed in plasma from a rachitic individual, does not.

Augmentation of positive phosphorus and calcium balances is the essential characteristic of all measures to prevent or cure rickets. The prevention seems to depend upon the correction of the calcium and phosphate deficiency of the blood, not upon direct action on physico-chemical local processes (Hunter). The plasma concentrations of phosphate and calcium are most easily and efficiently raised by the action of Vitamin D, which after either increases the amount of these minerals absorbed from the food, or diminishes their re-excretion into the intestine. The prevention or treatment of rickets, therefore, depends on obtaining a sufficient quantity of the antirachitic Vitamin. Cod liver oil, irradiated ergosterol (commonly sold as Viosterol), halibut liver oil, various irradiated foods containing ergosterol, direct summer sunshine or skyshine and artificial ultra violet light, all provide sources from which an adequate supply may be obtained. This treatment may be supplemented in severe cases by administration of phosphates or calcium salts by mouth.

(2) Late Rickets:—The disease occurs in children over five years of age and at puberty. It is similar in most features to infantile rickets in etiology, pathology and treatment, but the low serum calcium form is more common than the low phosphorus type. Tetany and osteoporosis are common, and, since the child is now more exposed than in infancy, fractures are frequent complications.

(3) Osteomalacia:—This condition, resembling late rickets, is nearly always found in women, and comes on in adult life after the epiphyses of the long bones have fused. In Canada, the U.S.A. and Great Britain it is rarely found, but occurs in many other countries, reaching its peak in frequency among the Mohammedans and high

caste Hindus, who observe purdah, in India, and among the middle class in certain parts of China, who spend a great deal of time indoors, but are not rich enough to buy good food. By far the greater number of cases begin during the third trimester of pregnancy, due to the excessive drain of mineral salts from the maternal organism by the foetus.

Dietary deficiency and lack of sunshine are the main etiologic factors apart from pregnancy. The low serum calcium form is the common type, but the low phosphorus variety also occurs. Tetany is a frequent complication. Due to the association with pregnancy, the disease was attributed to ovarian disfunction for some time, and ovarectomy was practised. There is very little evidence that the ovaries exert any effect on the disease apart from their role in pregnancy (Hunter). Plasma phosphatase is quite high in those cases so far examined, and the parathyroid glands are frequently enlarged, due, probably, to a compensatory hypertrophy.

Normal physiological resorption of bone occurs without the normal compensatory laying down of new bone, and, as a result, formerly hard bones becomes soft and flexible, and distortion of the bones of pelvis, chest and spine occurs. Muscular weakness and a characteristic waddling gait develop and spontaneous fracture may occur. but is less common than bending. At term Caesarean section is often necessary due to the deformed pelvis.

Treatment is similar to that for low calcium rickets, viz.:—Vitamin D plus calcium salts, but larger doses of cod liver oil or viosterol may be necessary. As much as 1.5 oz. of cod liver oil plus 1 Mg. of irradiated ergosterol per day with calcium lactate or calcium phosphate have been given.

(4) Hunger Osteopathy:—This is probably a form of osteomalacia of rare occurrence, and is due to extreme dietary deficiency. Men and women are affected equally, and the bones show more marked osteoporosis than in regular osteomalacia.

(b) DISEASES IN WHICH THERE IS A KNOWN METABOLIC DISTURBANCE—

(1) Generalized Osteitis Fibrosa of Von Recklinghausen:—"A disease which progresses with pain, fractures and disabling deformities, and is usually fatal. Widespread pathological resorption affects all the bones. There are multiple foci of osteitis fibrosa with or without benign giant celled tumours and cysts" (Hunter). The condition is twice as common in women as in men, and usually comes on in middle life. In the majority of cases, one or more of the parathyroid glands are found to be enlarged, but the severity of the condition bears no relation to the size of the tumour. The serum calcium is 12.6 to 23.6 Mg. per 100 cc., and the plasma inorganic phosphate is 1.0 to 2.0 Mg. phosphorus per 100 cc. The urinary output is high for both calcium and phosphorus, but especially so for calcium. The plasma phosphatase is increased up to more than 20 times the normal amount. The changes found in the bones are widespread resorption with thinning of the bones, fibrosis of the marrow cavities, the nests of osteoclasts and the cystic cavities; also greatly increased laying down of new bone in limited regions. Spontaneous fractures are common.

The real cause of the condition is still open to question, some regarding the parathyroid hypertrophy as primary and the bone changes as secondary, while a few regard the bony lesions as primary and the parathyroid enlargement as compensatory. Possibly the most generally accepted explanation is that with excess parathormone production the osteoclasts are stimulated to over-activity with resulting bone resorption, and that the local increases in bone deposit are due to stress and strain on the weakened bone.

Although parathyroidectomy has not yet proven to be a complete cure, it is the only promising form of treat-

ment, and is advised whether or not the parathyroids are palpable. When the parathyroids are not enlarged, extirpation is of doubtful value. Following removal of the enlarged glands, there is definite improvement in the symptoms, especially the pain. The plasma calcium and phosphate fall, the calcium and phosphate excretion diminish to normal figures, and there may even result hypocalcaemia with tetany. This latter condition is guarded against by postoperative administration of a high calcium diet and Vitamin D. When tetany occurs, it is easily controlled with parathormone, which becomes unnecessary in a very short time. The plasma phosphatase in most cases returns to normal, usually over a period of months. The X-ray picture of the bones changes only very slowly, and may show little improvement in a year.

There is a local condition "focal osteitis fibrosa," involving only one or several bones, which may be confused with the preceding disease. There is no change in bone away from the local lesion, and the phosphate calcium and phosphatase of the plasma are normal.

(2) Exopthalmic Goitre:—The concentrations of calcium and phosphate in the plasma are usually within normal limits, but the excretion of both is increased. Phosphatase is often above the normal strength in the plasma. In the bones there is frequently rarefaction by osteoclastic lacunar resorption, especially in the spongiosa and medulla, but also in the cortex of the bone.

(3) Nephritis:—In chronic nephritis with hypertension and uraemia there is commonly an excessive accumulation of inorganic phosphate in the blood plasma. The serum calcium usually shows a moderate decrease, but at times this is extreme. The proteins of the plasma are reduced and the protein - bound calcium similarly decreases accounting for the greater part of the fall in calcium concentration. There is no characteristic change in phosphate metabolism.

A concentration of more than 8 Mg. inorganic phosphorus per 100 cc. plasma indicates an early fatal termination in adults. For children the upper limit is 2 to 3 Mg. higher per 100 cc. In acute types of nephritis hyperphosphataemia is rare and in the nephroses it is of only moderate degree. "Hyperphosphataemia is almost invariably accompanied by low figures for carbon dioxide capacity" (Van Slyke and Peters). This does not mean that the phosphate increase is the chief contributing cause toward the acidosis, as it is usually only one among other more important acidogenic factors. The increased phosphate in the blood plasma is due in the main to the inability of the kidney to create phosphate.

(4) **Renal Rickets**:—This is a condition which is found at times complicating chronic nephritis, in which the bony changes resemble those occurring in rickets. The inorganic phosphate of the plasma is at first normal, although it may rise later on. The serum calcium may be somewhat low, but even when the (Ca) x (PO_4) product is normal, ossification is defective. Vitamin D has no curative action. Evidently there is some disturbance in endogenous metabolism of calcium and phosphorus due to the chronic nephritis.

(c) GENERAL BONE DISEASE OF UNKNOWN ETIOLOGY.

(1) **Osteitis Deformans or Paget's Disease**:—The etiology of this disease is at present little more than conjectural. In describing it Paget says, "There is tremendous resorption of bones associated with tremendous apposition completely altering the normal architecture, but apposition preponderates." It differs in character from generalized osteitis fribrosa in that this latter disease has excessive resorption with new bone being laid down only in isolated areas. Also the calcium and phosphate concentrations are normal or approximately so, phos-

phate and calcium excretion is approximately normal and there is no evidence of parathyroid disfunction. The only constant positive finding is a great increase in the plasma phosphatase which may increase to more than twenty times the narmal. The enzyme concentration is roughly correlated with the severity of the condition. There is at present no effective form of treatment.

(2) **Osteogenesis Imperfecta: (Fragilitas Ossium)**—This disease is present from birth and its chief features are fragile bones with liability to fracture and dislocation, blue sclerotis and, after 20 years of age, osteoclerosis with defective hearing. Multiple fractures often occur in utero and stillbirth is common. The bones are deficient in inorganic matter, but reliable figures for plasma concentrations and excretion of phosphate and calcium are not available. The phosphatase content of the plasma is sometimes, but not invariably, somewhat above the normal. Histologically the basic defect appears to be an inability to form osteoblasts. The condition is frequently mistaken for rickets, but anti-rachitic treatment is ineffective.

(d) DISEASE IN WHICH THE LESIONS ARE LOCAL IN BONE.

(1) **Fractures:** — During fracture healing the inorganic phosphate of the blood plasma rises (Harris & Tisdall). The same workers found, however, that the same rise occurred during a period of non-union of a fracture. Other investigators have found a similar rise in connection with reparative processes in other tissues than bone. Animals on a low phosphorus diet showed non-union of experimental fractures; on adding phosphate to their food ration healing occurred (Hunter). The significance of the rise in plasma phosphate following fracture is not yet certain and more experimental work is necessary. The plasma phosphatase shows no change.

(2) **Carcinoma in Bone:**—In this condition there is a variable increase in the phosphatase of the blood plasma.

(3) **Haematogenous Myelomatosis:** —The primary lesion in this disease is a new growth of bone marrow with decalcification by erosion. Both phosphate and calcium concentrations in plasma are raised above normal.

Thanks are again due to Dr. H. D. Kay for helpful criticism.

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Disease of the Gall Bladder.

By DOUGLAS TELFORD, B.A., B.C., '33.

Anatomy.

Gross Anatomy.—The gall bladder is a pear-shaped sac, somewhat bluish in color and has a capacity of nearly 50 cc. Lodged in a fossa on the under surface of the right lobe of the liver, it is in close relation to the liver, pylorus, duodenum, colon, right kidney, pancreas and diaphragm. It is well to bear in mind these relations since cholecystitis, especially if associated with peritonitis, is often confused with inflammation of these organs.

Little need be said about the exact anatomy of the duct system. The cystic duct leaving the neck of the gall bladder unites with the hepatic duct to form the common bile duct. The common bile duct then, in a well-known relation to the portal vein and hepatic artery, runs in the free margin of the gastro-hepatic omentum and finally terminates in the Ampulla of Vater in conjunction with the pancreatic duct The opening of the ampulla into the duodenum is surrounded by a much-discussed band of muscular fibres the sphincter of Oddi.

Several anomalies are met with in the extra-hepatic ductal system. First of all the gall bladder may be duplicated, but this anomaly is of little importance since the duplication occurs only once in several thousand cases. The cystic duct, however, may run parallel with the common bile duct and enter it at a very acute angle. The right hepatic duct may empty into the cystic duct.

Histology. The wall of the gall bladder consists of a mucous membrane, a thick layer of plain muscle and a peritoneal covering. The mucosa is thrown into graceful folds which, according to Boyd, are to be seen under the binocular microscope, "floating in the fluid like sea weeds in a marine pool." "The entire inner surface is divided into a series of polygonal spaces resembling little courtyards surrounded by high though delicate walls." The bases of these walls are richly supplied with blood vessels and lymphatics.

Blood Supply: The blood supply of the organ comes through the cystic artery which is usually a branch of the right hepatic artery. The venous return is by way of the cystic vein into the portal vein and not into an hepatic vein as might be expected.

Lymphatic Supply. The efferent lymphatics from the organ are joined by vessels from the liver and flow into mesenteric glands. Some of these glands are situated in the porta hepatis. One of great importance is located either at the neck of the gall bladder or on the cystic duct near its junction with the common duct. This is called the gland of the neck, or better, the sentinel gland because of its frequent enlargement in cholecysitis. Kadoma has proven by a series of injection experiments that there is a direct lymphatic connection between the first part of the duodenum and the gall bladder. He also has demonstrated that the lymph drainage from the gall bladder passes over the surface of the pancreas and does not enter its substance unless the two organs are adherent.

Nerve Supply. The gall bladder, like other hollow viscera, has a double nerve supply. The vagus is the secretory and motor nerve causing inhibition of the sphincter. The sympathetic through the ninth dorsal segment is the sensory nerve and causes contraction of the sphincter. It is essential to remember that the stomach, duodenum and gall bladder have a common nerve supply. Vagal reflexes from the gall blad-

der cause hyperchlorhydria and regurgitation while the inflammatory process of cholecystitis often extends to neighboring viscera, it is well to mention the innervation of the diaphragm through the 3rd, 4th, and 5th cervical segments. An appreciation of these facts will assist greatly inthe understanding of some of the symptoms and signs in cholecystitis.

Physiology.

Filling. The physiology of the gall bladder is not entirely clear. Bile is secreted continuously from the liver at a low pressure, about 300 m.m. of water. If the sphincter of Oddi can withstand this pressure the bile backs up the cystic duct past the valves of Heister and enters the lumen of the gall bladder. Thus we see that in times of fasting, the tonus of the sphincter being high, the gall bladder fills.

Emptying. .During periods of digestion, the sphincter of Oddi yields at a low pressure and the bile finds little trouble in entering the duodenum. But this is not the whole story. The gall bladder asserts itself at such times by expelling its contents in spurts. Preston demonstrated this beautifully. He isolated the portion of the duodenum containing the Ampulla of Vater and found that when the biliary tract was intact the sight or ingestion of food caused bile to be injected in jets at intervals of from 3 to 20 minutes. Fat, and to a lesser extent protein, cause the rapid emptying of the organ. Adrenalin and cholecystikinein produce powerful contractions, but stimulation of the vagus has no effect. Magnesium sulphate in the duodenum causes a relaxation of the sphincter and a profuse flow of bile into the intestine. Because of this and because of the theory that the gall bladder obeys the law of reciprocal innervation, i.e., that the relaxation of the sphincter is followed by contraction of the wall of the organ. Lyon developed his technique of non-surgical biliary drainage. By means of dye injections into the lumen and cholesystographic methods, it has been shown that magnesium sulphate, although relaxing the sphincter, does not cause contraction of the wall and that therefore Lyon's technique is founded on a false premise.

Interesting here, are the observations of Mann and Higgins, who have shown that in pregnant dogs and other animals, the gall bladder does not respond to the usual stimuli, i.e., a condition of stasis exists in pregnancy which disappears as soon as the uterus is emptied of its contents. Westphal has observed the same state of affairs and would like to explain the stasis on the basis of spasm of the neck of the gall bladder and sphincter of Oddi, a condition which he finds frequently in the early stages of pregnancy.

Storage. As has been mentioned a few minutes ago, the bile in times of fasting is stored in the gall bladder. The importance of this reservoir function is great and can be easily demonstrated by ligaturing the cystic duct. The bile then dribbles continuously and aimlessly into the duodenum regardless of the stage of digestion. Then again when both the cystic and common duct are ligatured, jaundice develops in the dog within 3 to 6 hrs., whereas, if the reservoir function of the gall bladder were in operation, jaundice would be delayed for 36 to 48 hours.

Concentration. When one considers that the gall bladder with a capacity of 50 c.c. is called upon to store many times this amount of liver bile, one realizes how great must be the concentrating power of this organ. The redundant mucosa is indeed efficiently constructed to carry on its work. Some writers say that by absorbing water and some bile salts the hepatic bile is concentrated as many as ten times. Graham's test for gall bladder function is dependent on this process.

In view of the functions of storage and concentration we may conclude that the gall bladder is valuable in maintaining a normal metabolism.

Gall Stones. No paper on cholecystitis is complete until the formation and structure of gall stones have been discussed. It is well then that we pause for a few minutes with this in view, considering first the chemistry of that fluid which Hippocrates included as two of the four cardinal humors.

Gall bladder bile is 80 to 90 parts water and 10 to 20 parts solids. The bile salts comprise over half the latter, while cholesterol, bile pigments and calcium account for the rest of the solids. The bile salts hold in solution both the cholesterol and the bile pigments.

Formation. It is evident, then, that any upset in the ratio of the solvent to the solute will result in precipitation of cholesterol or bile pigments and a resulting tendency to gall stone formation. This ratio may be disturbed in three conditions. (1) hypercholesterolemia, (2) infection, (3) stasis.

Hypercholesterolemia is a condition of excessive cholesterol in the blood and is present in typhoid fever, obesity, arterio-sclerosis and pregnancy. In the last condition the rise in blood cholesterol, starting at the second month of pregnancy and reaching a peak at the eighth month, at which time the concentration is 3 or 4 times normal. Thence it falls to normal by the 4th or 5th week post partum.

In the diseased gall bladder the same tendency to gall stone formation exists. The cholecterol of bile pigments this time remains at a normal level, but the bile salts are reduced in amount by the specific action of the bacteria. The cholesterol precipitates as such while the bile pigments, i.e., bilirubin united with the calcium of the bile and precipitates as calcium bilirubin.

Disease assists further in gall stone formation by providing the protein content of the calculi in the form of clumps of bacteria, leucocytes and desquamated cells. These form a nidus upon which the cholesterin crystallizes and the calcium bilirubin is deposited. These also form a protein framework or skeleton for the whole gall stone.

Stasis is the third condition which favors precipitation of the cholesterol and calcium bilirubin. Stasis is most likely to occur in the fat visceroptetic person living a sedentary life. This may be a relatively unimportant factor in gall stone formation, but when one hears of Mann and Higgins saying that stasis is a normal accompaniment of pregnant animals ,it makes one wonder.

Structure. Due then to one or a combination of two or more factors the formation of the metabolic or the infective stone results. The metabolic or pure cholesterol solitaire may be attributed to the perversion of metabolism known as hypercholesterolaemia. It is a silent stone of a radiant structure rarely giving rise to symptoms. Should it become impacted in the neck of the gall bladder an infection is likely to follow due to the acute stasis. The stone then rolling back into the organ will be surfaced by calcium bilirubin and become a type of mixed stone.

It is well here to mention the pure pigment stones which are frequent accompaniments of hemolytic jaundice. They are black and about the size of a grain of rice. They are multiple stones, the etiology of which is unknown.

The common mixed stones are due primarily to infection. They are composed of a protein nucleus and framework, and a body of cholesterol and calcium bilirubin. These are laminated stones with a facetted surface. They are multiple, forming a family. All the stones of one family are the same size, but there may be several families.

Incidence. Cholelithiasis very frequently complicates cholecystitis. In the acute catarrhs the incidence of gall stones is roughly 70%, while in the chronic, the incidence is from 75 to 95%, the chronic process.

Pathology of Cholecystitis.

In this paper only true inflammatory lesions will be discussed, including that

very interesting condition of the "strawberry gall bladder."

Incidence. The incidence of cholecystitis is very high. Some pathologists say that in routine examination of post-mortem cases, 66% of gall bladders present evidence of cholecystic disease. The predisposing causes are many. Significant among these are age and sex. The symptoms of gall bladder disease occur most commonly in the fourth decade or later, but younger individuals are not unaffected. Females, in the ratio of 2 to 1, some say 3 to 1, or 4 to 1, are more commonly the sufferers. Especially women who have borne children. In fact those who have experienced four or five pregnancies are "a safe bet" for cholecystitis. Putting this another way, Osler, quoting Naunyn, says, "90% of women having gall stones have borne children."

Etiology. The exciting cause of cholecystitis is due to an infection with micro-organisms. Bacteriological investigations have been many, and methods employed varied. Such men as Kelly and Deaver culturing the bile from diseased gall bladders, have found a high incidence of B. Coli and B. Typhosus, and only a very occasional streptococcus. These results can be quickly discarded when one realizes that the bile has a selective germicidal power and furthermore, who has proven that the bacteria from the diseased wall gain access to the lumen?

Rosenow made cultures of the ground up wall and has found the incidence of streptococci to be high, 40%, and that other bacteria as B. Coli, B. Welshii and Staphylococcus are also present.

A. L. Wilkie of Montreal, working along similiar lines, has made cultures from the bile, the whole wall and the wall stripped of the mucosa. He has found that the first two procedures give negative cultures for streptococci in practically every case, whereas the submucosa and muscularis stripped of its mucosa give positive cultures for streptococcus in over 40% of cases.

Dr. Magner of St. Michael's Hospital, agrees with the high incidence of strep., but claims that the whole wall, if properly washed of its bile, will give identical results to the wall stripped of its muccosa.

Wilkie has added a valuable bit of information by culturing the ground up cystic gland enlarged in cases of cholecystitis. He has obtained positive cultures for streptococci in 86% of cases.

These facts along with injection experiments which are soon to be discussed have established the streptococcus as the common etiological agent in cholecystitis.

Pathogenesis. There are five possible modes of infecting the gall bladder. (1) The infection may travel from the duodenum up the common duct into the gall bladder. This is conceivably possible, but is quite unlikely, because infection seldom travels up stream, and furthermore, bile is germicidal to pathogenic streptococci.

(2) The infection may travel from the liver to the gall bladder. This is a very reasonable theory in so far as it is common knowledge that the liver receives many bacteria from the intestine and spleen through the portal system and might well excerete bacteria into the bile. This theory falls into disrepute, however, on the same grounds as the first. Bile is germical to most bacteria save certain ones, such as the typhoid bacillus.

(3) Assuming again that many bacteria reach the liver by the portal circulation, some must escape and travel by way of the lymphatics to the gall bladder. This is a popular theory. Evarts Graham, in a series of 30 cases of cholecystitis, found accompanying hepatitis in every instance. Magner favors this theory especially since injection of streptococcus, directly into the portal vein or directly by way of the appendicular vein has produced cholecystitis in nearly 50% of cases.

4. Rosenow and Wilkie claim there can be no doubt that bacteria reach the

gall bladder by way of the blood stream. They have produced cholecystitis in 40% of cases by injecting strep. into the ear vein of the rabbit. Horeman and Magner and others have failed to duplicate these results and admit of the feasability of this route only from such sources as the tonsil.

(5) Cholecystitis occasionally develops through a direct extension of the inflammatory process from adjacent viscera.

In summary, then, the gall bladder is commonly diseased by one of two routes—the haematogenous and the lymphogenous from the liver, the former being the path of choice if the focus is the tonsil, etc., and the latter the path of choice if the focus lies in the appendix, intestine, spleen, etc.

Pathological Anatomy. The inflammatory process may be acute or chronic. If acute the cholecystitis may reveal itself in many forms from the catarrhal to the acute suppurative. In the former there is little to be seen by the naked eye beyond congestion and edoema. In the latter a very acute process is evident. The organ may be distended with pus, particularly if the outlet is obstructed by a stone. This pus may be bile stained or even blood stained if the empyema is of recent occurrence. The whole wall may vary from a bright red to black patches if gangrene is present. The peritoneal surface may be covered with an inflammatory exudate and be adherent to omentum or to adjacent viscera. The regional lymphatic glands, invariably the cystic gland, are enlarged and may contain pus.

Microscopically a typical acute reaction is evident and some of the surface epithelium is desquamated.

Chronic cholecystitis may be the end result of an acute process or it may come on gradually and insidiously. Sometimes the pathological changes are so slight that it is impossible to realize how the organ could be responsible for the symptoms of the case. One of the earliest signs is a loss of the normal bluish lustre. The wall soon becomes thickened. An excess subserous fat may appear and the cystic gland enlarges.

On opening the sac the mucosa is oedematous and discolored. The beautifully thin villi have become swollen, debased and eroded, especially if stones are present. The depressions between the villi may be decidedly deepened and gland-like in appearance, while the surface epithelium is often distended with mucus. The outer coats become thickened and the muscular and elastic tissue become replaced by scar tissue. Thus an inert bag is formed with a lining of interlacing bands of fibrous tissue which in turn disappear to give a smooth surface.

When the scar tissue involves the cystic duct so as to occlude it, the condition of hydrops of the gall bladder may follow. The cavity is distended by a clear watery fluid which has been secreted by the mucosa.

Another type of diseased gall bladder is that first described by Moynihan and descriptively called by MacCarty, the "strawberry gall bladder." "The reddened mucosa is studded with tiny yellow spots suggesting seeds of a ripe strawberry." Boyd has observed this under the binocular microscope and has found the folds of mucosa "loaded down by dense yellow opaque masses as a delicate birch tree might be weighed down by the winter's snow." In a few cases the lipoid or cholesterol material has accumulated in large polypoid masses which some think may separate to form nuclei of gall stones. This interesting condition is invariably associated with inflammation. As such it may be the result of the inflammation or it may be just another expression of that perversion of physiological activity, hypercholesterolemia.

Complications. Just a word must be added regarding the common complications of cholecystitis. First the acute gall bladder may perforate, resulting in fistula or abscess formation or general peritonitis. Second—the infective process may spread to any part of the so-called gastro-duodeno-hepatica-pancre-

atic system. The frequency with which hepatitis, pancreatitis and duodenal ulcer color the picture of choleystitis bears out the latter statement.

Conclusion.

In this paper, I have sketched the anatomy, physiology and pathology of the gall bladder. Furthermore, I have attempted to correlate certain opposing theories and to leave the reader with at least one reasonable solution for most of the problems. In so doing, I fear that certain topics of current interest have been overemphasized while others perhaps of more vital importance have been dismissed with a few remarks. I trust, nevertheless, that the interest resulting has outweighed the detail omitted.

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Calcium in The Body.

By I. C. SHERMAN, '33.

Calcium metabolism is a subject about which a great deal has been written and many controversial opinions aired. One great stimulus was given to its study by Collip in 1925, when he made his extract of the parathyroid gland, known as parathormone. This was intimately bound up with the study of calcium metabolism. The other came a few years later, when it was shown that the antirachitic factor—Vitamin D and ultraviolet irradiation—had a functional relationship to the parathyroid glands and calcium metabolism.

Functions of Calcium.

1. *Bone Formation.*—Calcium exists in bone chiefly as the tertiary phosphate (Ca_3 $(PO_4)_2$—83% to 90%) and the remainder as the carbonate— $CaCO_3$. The manner in which the calcium is deposited is by no means agreed upon. Robison explains it by enzyme action. He has shown the presence of a phosphatase in the epiphyses of growing bones which is capable of splitting the hexose phosphate of the blood into hexose and inorganic phosphate. The concentration of phosphate-ion in the bone increases and is precipitated with calcium as calcium phosphate. As Cantarow points out, none of the theories of ossification take into consideration the part played by Vitamin D or the parathyroids, and it is likely that an explanation involving these two factors will be closer to the truth.

2. *Membrane Permeability.*—It has been shown definitely that sodium increases the permeability of a cell membrane, whereas calcium diminishes the permeability. The antagonistic actions of these two ions was well illustrated by Bayliss, who concluded that an increase in permeability of a membrane was an intimate part of the excitatory process, and inhibition, as the opposite process was thus associated with decrease in permeability. This action has been attributed to a consolidating or ctabilizing effect of Calcium upon the colloidal systems as opposed to the liquefying tendencies of sodium and potassium.

3. *Cardiac Action.*—If a heart be perfused with an excess of calcium in the perfusion fluid it will contract well,

but its relaxation will decrease progressively and the beats become steadily smaller in extent. The heart finally stops in systole, which is called calcium rigor. Sympathetic stimulation produces an effect similar to that of calcium and it has been suggested that such stimulation liberates calcium. It may be that the calcium is concerned in the transformation of chemical energy into muscular action because in the diastolic standstill produced by withdrawal of calcium the excitatory process still goes on and glucose is still consumed.

4. *Coagulation of Blood and Milk.*—It is generally accepted that calcium activates prothrombin in the presence of thromboplastin or thrombokinase. In the present theory of blood clotting it is considered that the latter neutralizes anti-prothrombin and allows the calcium to join with prothrombin to form thrombin. The thrombokinase of Morawitz and others is not a kinase or enzyme, and Howell has identified it as cephaline. It is now called the phospholipine factor. Calcium is essential in this process and is sometimes given preoperatively to increase the coagulability of the blood.

When milk enters the stomach the caseinogen is converted by rennin into casein in which the presence of calcium salts is precipitated as insoluble calcium caseinate. This constitutes coagulated milk.

5. *Nerve Impulses*—Calcium is necessary for the passage of a nerve impulse across a myoneural junction as well as across a synapse.

6. *Nerve and Muscle Excitability*—Calcium and magnesium are known as the sedative ions, whereas sodium and potassium are the irritative ions. Calcium and magnesium salts depress nerve and muscle irritability. Calcium acts similarly upon striated and unstriated muscle and upon the voluntary and autonomic nervous systems. It is thought, however, that the calcium ions are more concerned with sympathetic activity. The effect on the neuromuscular system is readily seen in parathyroprivic tetany where an injection of $CaCl_2$ quickly stops the hyperexcitability.

7. *Bloodvessels and Capillary Permeability*—Calcium-ions increase vascular tone by causing vasconstriction. It has also been found that they decrease capillary permeability. This has led to the use of calcium salts in counteracting certain types of edema, because increase in capillary permeability is one of the important factors in edema. Calciumtherapy seems to be of distinct value in inflammatory edema and in urticaria.

8. *Acid-base Equilibrium*—Calcium is of minor importance in the regulation of the reaction of the blood and the tissues. This has been more adequately proven in experiments with the parathyroid hormone where great variations in the serum-calcium level have occurred with no demonstrable disturbance in acid-base equilibrium. The H-ion concentration affects the ionizable calcium, but evidence in regard to similar variations in serum-calcium is contradictory.. Cantarow sums up the situation as follows: "In spite of minor changes in serum- calcium concentration, which may possibly occur with alteration in H-ion concentration, it appears doubtful that this element exerts any significant influence upon the reaction of the blood and tissues." At most, the part played by calcium in the neutralization of mineral acids is very small.

9. *Water Balance*—Calcium probably plays a small part in the preservation of normal water balance because it exists in very low concentrations. Its effects are exerted upon the permeability of capillaries and upon the hydration capacity of colloids. Both of these depend upon the consolidating effect of calcium upon colloidal systems.

State of Calcium in the Blood.

Calcium determinations are made upon *serum*, *plasma* and *whole* blood. The most reliable serum-calcium, because it is most easily determined. In

the normal human subject it is fairly well accepted as being 9-11 mgm. per 100 c.c. of serum. The plasma calcium levels given by different authors vary considerably. Stewart and Percival give it as 10%—15% higher than the *serum* but more recent estimations place it as 0.5 to 1 mgm. per cent. lower than serum-calcium. It is of interest that the calcium content of red blood cells is very low, and hence the whole blood calcium is lower than that of serum-calcium. The level of whole-blood calcium is not very well agreed upon. Kramer and Tisdall state it to be 5.3—6.8 mgm. per 100 c.c. of whole blood.

The serum-calcium is of the greatest importance, and only it shall be referred to in the following discussion. It is divided into two parts.

A.—*Diffusible Fraction*—That part which is capable of passing through a capillary wall or cell membrane. It is normally between 4.5 and 5.5 mgm. per cent. According to Cameron and Moorhouse, the total calcium of the spinal fluid represents the diffusible calcium of the plasma. This they give as 5—6 mgm. per cent. This observation has proven of some value in studying diffusible calcium in different clinical conditions.

Diffusible calcium is divided into two parts.

(1) Ionized—which is probably never more than 2 mgm. per cent.

(2) Un-ionized—which constitutes the remainder and is in both organic and inorganic combination.

Because the ionic calcium appears to be but a small fraction of the diffusible calcium, Greenwald proposed the view that some of the calcium is bound to an organic substance in a "citrate-like combination," the compound being intimately connected with the parathyroid hormone, probably diffusible and slightly ionized. This is generally discredited.

B.—*Non-diffusible Fraction* — That part of the calcium which cannot pass through a capillary wall or cell membrane. It is completely un-ionized and is given as 4.7—5.7 mgm. per cent. The nature of the combination responsible for this is subject to much controversy, but is known to be definitely bound to serum protein. In nephrosis or nephritis with edema, calcium is low, due to loss through the kidneys of serum-albumen and serum-globulin, carrying with them non-diffusible calcium. In some cases of advanced nephritis with uremia and phosphate retention, the serum-calcium may be increased. The only explanation here is that the increased H-ion concentration present in such cases will raise the calcium by reason of an acidosis, although it seems questionable that under ordinary circumstances increased acidity can accomplish this effect. It is even said that the calcium is withdrawn from the bones in order to help the deficient alkali reserve. This is a very doubtful theory in view of what has already been mentioned regarding calcium in acid-base equilibrium.

The diffusible and non-diffusible fractions may vary independently of each other, and it appears likely that if they are in equilibrium at all it is with but a small fraction of the former. It should also be remembered that the ionized calcium may vary independently of the serum-calcium. An instance of this is seen in tetany of hyperpnoea where alkalosis is produced and the total serum-calcium is normal but the ionized-calcium is decreased.

Calcium Absorption.

The daily requirement of calcium in the adult has been given by Sherman as from 0.4 to 1 gm. per day. The calcium intake should be at least 1 gm. of calcium for every 100 gms. of protein. Since one pint of milk contains approximately 1.06 gms. of calcium, this is equivalent to 1 pint of milk per 100 gms. protein. During growth, pregnancy and lactation this must be increased, for unless the supply be adequate the calcium reserves of the bone

are drawn upon, and this may result in decalcification. The absorption of calcium occurs in the small intestine. It is governed by three factors.

(1) *H-ion concentration within the intestine.*—Irrespective of the type of compound which is administered orally calcium is probably absorbed in the ionized form (Collip). Consequently, the more soluble the compound and the higher the H-ion concentration of the intestinal contents, the greater is the absorption. The intestinal contents are normally acid for a considerable period of time following the introduction of food. As the acid chyme approaches neutrality the phosphate and carbonate ions tend to combine with calcium, and when the pH rises above 7 the calcium is precipitated in the form of the tertiary phosphate, and to a lesser extent as the carbonate.

The soluble calcium salts are the chloride, lactate and gluconate. They are more assimilable than the phosphate or carbonate. Administration of sugars, e.g., lactose, increases the calcium absorption. Bergeim claims that this is due to the formation of lactic acid which produces an acid condition in the intestine.

(2) *Relative proportion of other substances in the diet.*—This group includes those which affect the absorption by other means than through the H-ion concentration of the intestinal contents. In an excess fat diet, the fatty acids combine with calcium to form insoluble soaps, which are poorly absorbed. Thus the low calcium is not due to an increased excretion but to a lowered absorption. According to Cantarow, excessive amounts of phosphorus lead to the formation of insoluble tertiary phosphate which cannot be absorbed. But it has been found in the Toronto General Hospital that even when the phosphorus in the diet is high the absorption of calcium is not hindered.

(3) *Vitamin D*—This causes an increased retention of calcium. Some authors claim it directly influences the absorption process for calcium and phosphorus by playing a definite regulatory action upon the normal functioning of the mucous membrane of the small intestine. It is said that a deficiency of Vitamin D lowers the ability of the musoca to absorb calcium and phosphorus. This has recently been doubted by Bergeim, who attributes its value to the effect upon the intermediary metabolism of calcium and phosphorus at the epiphyses. Cantarow also leans towards this opinion, and says that the loss of calcium in rickets is not due to diminished absorption, but probably due to some abnormality in intermediary metabolism of these elements. It seems that the latter theory has greater attractions than the former.

Calcium Excretion.

Calcium is actively excreted by the lower ileum, colon and kidneys. Normally 70%—90% is excreted in the faeces and 10%—30% in the urine. Faecal calcium represents both unabsorbed calcium of the food and re-excreted calcium. On a diet very low in calcium the excretion is markedly reduced but not completely suppressed. The calcium reserves are drawn upon to maintain the normal level of blood calcium. The trabecular portion of bone is the storehouse which is called upon first and the shafts are drawn upon later. There are five factors involved in calcium excretion.

(1) *Thyroid*—Increased activity of the thyroid gland increases the excretion due to a general action of all the tissues resulting in a rise in the metabolic rate.

(2) *Parathyroid*—Administration of the extract results in an increased elimination of calcium. A similar effect is observed in a tumor of the parathyroid gland known as Von Recklinghausen's disease. The increase takes place entirely in urinary calcium and faecal excretion is unaffected. Greenwald and Gross have found that the reverse is

also true — i.e., calcium eliminated is diminished after parathyroidectomy.

(3) *Vitamin D*—Deficiency in this decreases calcium retention whether the effect is upon the intermediary metabolism of calcium or upon the absorptive power of the small intestine. The increase in calcium excretion is accompanied by loss of phosphorus and takes place in this case by way of the gastro-intestinal tract. This is one reason why it is claimed that effect of Vitamin D is upon the intestinal mucosa causing a decrease in absorption, rather than acting elsewhere and causing an increased excretion.

(4) *Excess of certain inorganic elements*—especially phosphorus. They may bind the calcium in an insoluble form in the gut, but this is doubtful.

(5) *H-ion concentration*—A change to the acid side of the acid-base equilibrium leads to decalcification and therefore increased elimination of calcium. This is readily seen by the Feudenberg-Gyorgy equation, where a rise in H-ion may easily cause a fall in calcium-ion in order to maintain the constant. This elimination occurs largely by means of an increase in urinary calcium. This has been used in the treatment of lead poisoning. Excretion of lead parallels excretion of calcium, and when ammonium chloride is given the tendency is towards acidosis, and both lead and calcium are excreted.

Relation of the Antirachitic Factor to Parathyroid Function.

The antirachitic factor in the practical sense includes three elements — foods containing Vitamin D, irradiated ergosterol and ultraviolet light. It is quite generally agreed that a certain minimum of this factor is necessary for retention of normal amounts in the body. This holds true for small doses only, as is pointed out by Taylor, Weld, Branion and Kay. The source of their antirachitic factor was irradiated ergosterol. In their experiments they found that when the dosage was increased to an excessively large degree, there was a very close association between the action of the sterol and parathyroid function. This relationship is thought to be a direct stimulation of the parathyroid tissue by overdosage of sterol, resulting in, not a retention, but a loss of calcium from the body. The effect of Vitamin D upon calcium metabolism therefore becomes reversed at a certain dosage, and a parathormone-like action becomes manifest. This action consists in the liberation of calcium from its store-houses in bone. The symptoms and post mortem findings following overdosage with irradiated ergosterol are indistinguishable from those resulting from the administration of lethal doses of parathormone. The precise level of dosage for this reversal effect has not yet been determined. Since little is known of the effect of small doses of parathormone, they left this consideration out of their experiments. It is unknown whether small doses cause calcium retention just as do small doses of irradiated ergosterol, and thus it may even be that there is some relation between these two. They indicate that there may be some clinical significance in this study in cases of hypervitaminosis. Some writers claim that the overdose must be so great that this is negligible as a clinical entity. Taylor et al hold this view to be erroneous, because the experiments have been performed largely upon rats and other species of rodents which are highly resistant to the toxic action of the sterol. Dogs, on the other hand, react to parathormone in doses of the same magnitude as those which influence the calcium and phosphorus metabolism of the human subject. In adult dogs they found that death occurred following the administration of irradiated ergosterol when the amount given per kilo had a greater potency than twenty times that of the maximal therapeutic dose. Thus we see that the production of hypervitaminosis with its parathormone-like action may not be so difficult

in the human if care is not taken with the dosage.

Relation of Calcium Metabolism to Tetany.

The following tetanies are related etiologically to a primary disturbance of calcium metabolism: (1) parathyroprivic (post-operative parathyroid), (2) adult and juvenile idiopathic, (3) infantile, (4) osteomalacic, (5) tetany complicating sprue and coeliac disease in infants. The one common factor in all of these is the low serum-calcium. As a rule, when the serum-calcium falls below 7 mgm. per cent. symptoms of tetany are manifest. The factor which determines the actual development of tetany is not the level of total serum-calcium, but rather the amount of diffusible calcium or the concentration of calcium-ions. One draw-back in being able to settle the question conclusively is that at present there is no satisfactory method of determining the concentration of calcium-ions. In an extensive review of the subject, Cantarow concludes that tetany is a definite symptom complex dependent upon a decreased concentration of calcium-ions, and the effect of all tetany-producing agencies is exerted through their capacity for diminishing this concentration. There are other forms of tetany not dependent primarily upon a disturbance of calcium metabolism. In these, we also find the low concentration of calcium-ions in the serum. The more important of these are:

(1) *Hyperpneic Tetany*—Collip and Backus showed alkalosis and tetany could be produced by hyperventilation. There is no demonstrable alteration in the level of serum-calcium, and, as he states: "There may be no essential difference between true parathyroid tetany due to lowered calcium content of the blood and the tetany of overventilation, or of alkalosis, associated with a normal blood calcium but a diminution in ionization due to an increased pH."

(2) *Gastric Tetany*—This is associated with an excessive loss of HCl in the vomitus. This results in an alkalosis, and, as above, we find no actual change in level of serum-calcium, but there is a decrease in the amount of ionized calcium.

(3) *Phosphate Tetany*—Singer succeeded in producing hypocalcaemia and symptoms resembling clinical tetany by injection of neutral and alkaline phosphates. This increase in phosphates causes more tricalcium phosphate to form and so decreases the ionized calcium.

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Antony Van Leeuwenhoek and Some of His Microscopic Observations.

By L. PEARLMAN, '34.

NOTE: 1932 marks the three hundredth anniversary of the birth of Antony van Leeuwenhoek.

It is generally conceded that many of our great men in medical history can lay claim to fame through more than one channel. Thus, Leonardo Da Vinci goes down to posterity not only as a consummate artist, but also as an anatomist of marked ability. Again, Louis Pasteur is honoured alike in chemical and medical circles. Similarly, Antony van Leeuwenhoek is recognized not only as the discoverer of bacteria, but also as the progenitor of other original discoveries less well known.

It is proposed in this paper to bring to the reader brief summaries of but a few of these lesser discoveries. Consequently, the story of the discovery of bacteria (1675) will be dismissed with the suggestion that an account of this work may be found in any authoritative bibliography on the subject.

Leeuwenhoek was born in Delft, Holland, in 1632, of a family of brewers and basket-makers. He spent the first sixteen years of his life in comparative opulence. The death of his father, however, interfered with his education; and Leeuwenhoek became successively a clerk in a linen store, and a very unsuccessful merchant. So markedly was he lacking in business acumen, that he was found at the age of twenty-eight a municipal employee —"chamberlain of the sheriff,"—with the following duties: "To open and shut the door of the council chamber both on ordinary and extraordinary days of meeting; to show honour and respect to the councillors; to keep inviolate anything he might hear in the chamber; to keep the chamber clean; to make the fires, also to preserve the place from fire, and to do all that a good and faithful chamberlain should do." In short, at a salary of $125 per annum, van Leeuwenhoek was the janitor to the town hall.

If this illuminating position did not add to his prestige, it at least gave him ample leisure to pursue a hobby. Probably guided by a childish desire to make things look bigger, and thus satisfy an inherent curiosity as to the structure of the various objects surrounding him, the unimaginative Dutchman took to the unusual pastime of grinding lenses. This ultimately led to his becoming so skilful, that the four hundred and nineteen lenses and two hundred and forty-seven simple microscopes which he constructed during his long lifetime were regarded by contemporaries as some of the finest examples of the lens-grinder's art.

Being thus supplied with superior instruments, Leeuwenhoek began examining and making marvellously accurate observations upon hundreds of specimens. These observations varied from attempts to investigate the contents of muddy water to the examination of the histological structure of the cornea. It was in the course of these rather diversified microscopic wanderings that he made his exceedingly large number of discoveries. These important finds were first known only to himself and a restricted circle of scientifically inclined acquaintances.

Among the select group he permitted to peep into his microscope (and this under his own supervision, since he was very jealous of his instruments) was Regnier de Graaf. After much coaxing, de Graaf finally induced the

suspicious Dutchman to send accounts of his novel observations to the recently formed Royal Society of London.

Leeuwenhoek's first communication to the Society on the structure of a bee and a louse was met with enthusiasm. Eventually, in 1680, when the Society had become favourably impressed with his observations in the field of microscopy, Leeuwenhoek was elected a Fellow. In appreciation of this honour he wrote them a rather formal letter in which he promised them 26 of his finest microscopes — after his death; for, throughout his entire life, he stubbornly refused to part with a single instrument, or, for that matter, would he even reveal the secret of his facility at grinding lenses.

Among his 375 papers and letters to the Royal Society, was one which would indicate that he was at least a precursor to the discovery of the Virchow-Robin spaces in the pia mater. In his descriptions of the blood vessels in that membrane, he points out that the blood vessels visible to the naked eye are further sub-divided into vessels of "an admirable and incredible fineness," which he exposed by removing the pia from the brain. Continuing, he observed further that "the said veins which run through the thin membrane disseminate their ramifications through the brain, after the manner as vines lying upon the earth shoot roots into the ground; imagining the brain to be like the earth and the veins like the roots in it."

Since Leeuwenhoek was haphazard in his choice of material for microscopic examination, it is not surprising to learn that he jumped from the study of neurological specimens to observation of muscle tissue. Indeed, he is credited with the first description of striated muscle. He noted the arrangement of the fibres in fasciculi, and, obtaining a single fibre, his first conclusion was that the muscle was made up of "very small conjoined globules." Further consideration, however, convinced him that they were "rimples." He explained the striations as "caused by the various falling of light upon these rimplings, of the small strings of which every bundle of muscular fibres consists."

Embryology received its contribution in the form of Leeuwenhoek's original observations in 1678 on spermatozoa. It will be observed that this work followed on his bacteriological investigations. Because of the property of motility common to both, the bacteria and the spermatozoa, Leeuwenhoek considered the latter to be animacules as well. The subject of generation and the part played in it by the spermatozoa was one on which Leeuwenhoek wrote prolifically. But this, unfortunately, revealed him as an observer rather than a scientist, because Leeuwenhoek was able only to see and to observe, but not to arrive at conclusions based on previous knowledge or experience in scientific endeavour.

He was convinced that the spermatozoa were produced in the testis, but refused to acknowledge de Graaf's observations on ova. Indeed, he formulated his own theory on generation. He pointed out that after innumerable dissections of many female mammalia, he never once had seen anything larger than a red blood cell in either the Fallopian tubes or the remainder of the genital tract. He therefore argued that it was inconceivable for a Graafian follicle (!) to even enter the ostium of the latter. Hence, the female could serve only as a source of nourishment to the spermatozoon, which itself was the generative power, and was merely lodged in the uterus. If the spermatozoon failed to find a suitable place in the uterus from which it could obtain nourishment; or, as in the birds and amphibia under his observation, the "animalia seminis masculi" (as the spermatozoa were called) failed to gain entrance into the egg, they starved to death, and consequently further formation of a new individual ceased.

In the light of later research, Leeuwenhoek's theory of generation is somewhat crude; but coming from this uneducated observer, it had some reasonableness in it, and at the same time showed that de Graaf's theory of the ova was also incomplete. Neither theory established the relationship which linked the ova and the spermatozoa in the generative process.

Turning now to the history of physiology, Leeuwenhoek's influence is very prominently displayed, for it was he who first described the red blood corpuscle. It was while working with frogs that he observed in the blood of these creatures floating globules of a pale colour. These he saw being carried in the blood vessels of different sizes. He speaks of the globules as "soft fluid corpuscles, many of which lie on one another; they unite close together, by which conjunction the blood under its surface alters its colour and becomes dark red or blackish. The same red globules, when they are single and stick within to the sides of very slender glass tubes, will appear white and colourless" — from all of which he concluded that the bi-concave "oval-shaped discs," as he later calls the corpuscles, gave the blood its characteristic hue. He further pointed out that "these sanguineous globules in a healthy body must be flexible and pliant to pass through the small capillary veins and arteries," giving as proof the observation that "in their passage, they change into an oval figure, reassuming their roundness when they come into a wider space."

In pursuing the study of the red cells and using them as a means of observing the direction of flow of blood, Leeuwenhoek ultimately realized and accurately described capillary circulation. Although Malphigi is generally credited with the discovery of this phenomenon, some writers are prone to believe that Malphigi never fully grasped the significance of the capillaries he had seen; whereas Leeuwenhoek, who worked independently of, and subsequent to, Malphigi, gave the first truly reliable description of this sequel to William Harvey's work. There can be no doubt, however, that Leeuwenhoek had a very clear conception of the whole subject.

No better verification of this can be had than a quotation from his letter to the Royal Society. His observations were made on frog tadpoles, using first the gills and later the tail. "For I not only saw that the blood was driven in many places through very thin vesels, from the middle of the tail to the outside of it, but also that each such vessel was bent in a curve and carried the blood back to the interior or thickest part of the tail in order to convey it to the heart. So that it appeared to me that the blood vessels observed in this animal and called arteries and veins, are exactly alike; only they can be called arteries when they carry the blood to the utmost extremities of the small blood vessels, and veins when they carry the same blood back to the heart."

The definitions of artery and vein which Leeuwenhoek thus originated still hold to-day. From the extract quoted it is obvious that his ideas on the capillary circulation were complete and accurate.

In 1723 Leeuwenhoek died, being then ninety-one years old. His long life was ever filled with the paramount desire to see more of the hitherto hidden mysteries of the microscopic world. No better attestation to the success he attained in this can be had than a reference to the records of his labours.

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Statistical Review of the Mortality of Pernicious Anaemia in Toronto, 1923 - 1931.*

A review of mortality statistics for Toronto discloses a remarkable change in the death rate for pernicious anaemia since the important discovery of the benefits of liver therapy in 1926 by Minot and Murphy, for treatment of patients afflicted with this disease.

Having in mind certain influencing factors, such as the tendency toward better diagnosis, difference in method of classification of causes of death, etc., the death records for pernicious anaemia in Toronto and elsewhere are none the less indicative of the great value of this new therapeutic agent.

In Toronto, in 1927, the year immediately following its introduction the death rate for this disease was reduced by nearly one-half, and the new lower rate has more or less maintained throughout the past four years.

Mortality from Pernicious Anaemia, Toronto, 1923-1931 inclusive.
Death Rate per 100,000 Population.

Year.	Deaths.	Rate.
1923	69	12.8
1924	79	14.6
1925	69	12.6
1926	83	14.9
1927	44	7.7
1928	40	6.8
1929	41	6.8
1930	59	9.5
1931	44	7.0

For purposes of comparison between the two periods of time, before and after the use of this new treatment. and in order to illustrate more effectively the substantial reduction that has taken place in the pernicious anaemia death rate, the years 1923-1926 inclusive, and 1928-1931 are combined to make two four-year periods. The exclusion of 1927 is noted, but the effect of the inclusion of this year would result in differences of rates which would be of a negligible quantity. From the above table we find a total of 300 deaths attributed to this disease during the period 1923-1926, which number represents a rate of 13.7 deaths per 100,000 population, while in the latter period, 1928-1931, the number was reduced to 184, or a rate of 7.5. This marks a reduction in the death rate of over 45 per cent. following the introduction of this new form of therapeusis.

A consideration of the percentage of total male deaths and total female deaths by certain age groups, reveals interesting changes which appear similar to those that have taken place in the statistics for diabetes mellitus after medical research had produced the insulin treatment. A prolongation in life is significant in the mortality records for both of these diseases.

In the case of pernicious anaemia, comparison between the two selected periods shows that following liver therapy, 6.3 per cent. more males and 12.9 per cent. more females at time of death have attained the mark of fifty-five years of age or more.

Excluding the more extreme ages at either pole of the life span, in which the occurrence of pernicious anaemia is more or less uncommon, we note that between the ages of 25 and 84 years of age the average at death has increased thus far 3.6 years in males and 4.5 years in females. In order to find the ages at which this disease is most prevalent, specific death rates are shown for age groups between 35 and 79 years of age. Above and below

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Percentage of Total Male and Female Deaths Attributed to Pernicious Anaemia by Certain Age Groups.

Sex.	Period.	AGE GROUPS. Under 35.	35-54.	55-74	75 and over.	Total.
Both	1923-1926	4.7	24.7	59.3	11.3	100.0
	1928-1931	3.3	15.8	63.6	17.3	100.0
Male	1923-1926	5.6	21.6	60.0	12.8	100.0
	1928-1931	3.0	17.9	61.2	17.9	100.0
Female	1923-1926	4.0	26.8	58.9	10.3	100.0
	1928-1931	3.4	14.5	65.0	17.1	100.0

these ages the mortality is so low as not to warrant consideration.

Specific rates are those based upon the number of deaths occurring among every 100,000 estimated population in certain age groups. These rates show throughout higher rates for females; they also indicate substantial reductions when comparison is made of the rates between the two four-year periods.

for ages 65-79 years, the group which produces the highest rate of mortality from pernicious anaemia, we find that the specific rate for males is 36 per cent lower, or more than double the percentage decrease for females.

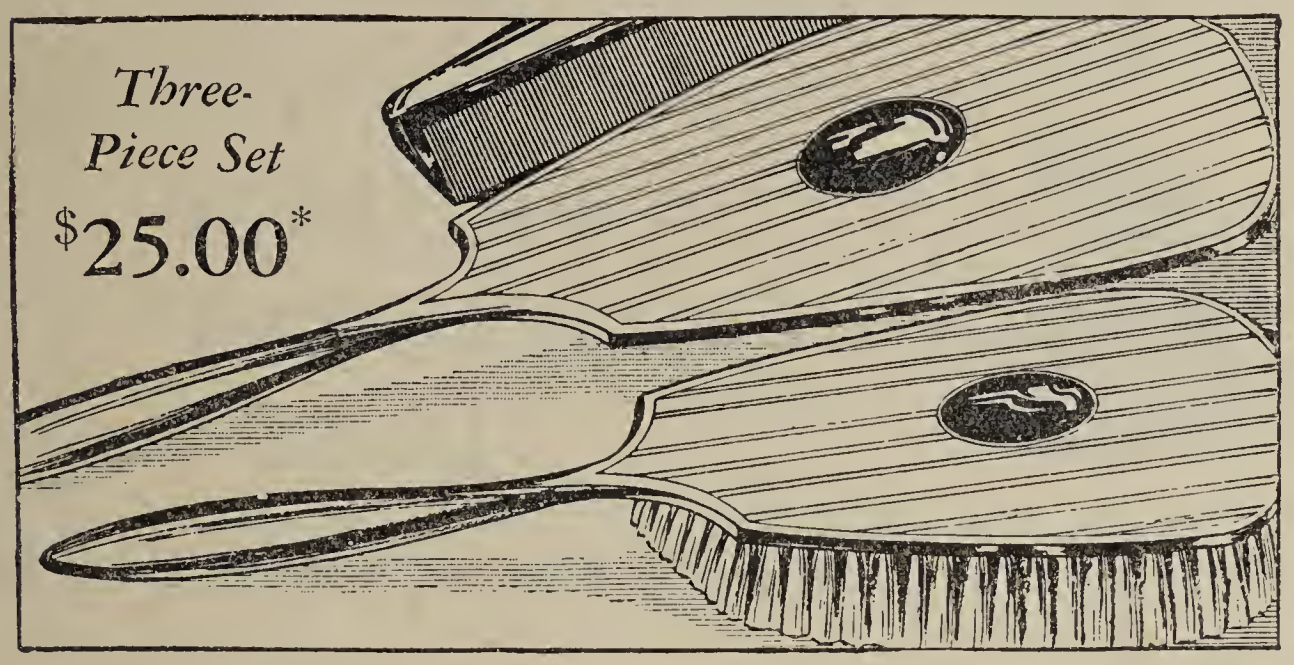
To sum up: In the foregoing statistics relating to this disease, which apply only to Toronto, it would appear that with the introduction of liver therapeusis the mortality rate has been

Mortality from Pernicious Anaemia.

Specific Death Rates per 100,000 Estimated Population Living in Certain Age Groups, by Sex.

AGE GROUPS.	TOTAL. 1923-26.	TOTAL. 1928-31.	MALES. 1923-26.	MALES. 1928-31.	FEMALES. 1923-26.	FEMALES. 1928-31.
35-39	4.0	.5	1.0	nil	7.1	.9
40-44	8.2	1.7	6.3	1.1	10.1	2.3
45-49	15.3	6.5	14.6	7.3	16.1	5.8
50-54	32.7	13.8	23.9	10.7	40.9	16.6
55-59	57.3	28.1	51.5	25.6	62.5	30.3
60-64	74.9	33.5	70.2	22.0	78.9	43.5
65-69	105.8	92.4	103.1	71.8	108.2	110.2
70-74	203.2	116.5	172.4	81.3	228.1	145.0
75-79	212.3	190.3	209.8	172.3	214.1	203.9

From the point of age grouping, if we consider the specific rates for ages 35-49 years inclusive, a greater reduction is shown for females than males. The percentage reduction in the female rate is 75 per cent., as compared with 64.5 for the male specific rate. Above the age of 49 years, we find a greater reduction in the male rates. For males 50-64 years, the percentage reduction is 58.9 as against 51.5 for females; substantially lowered; that the mortality among females is considerably higher than among males; that the reduction in mortality has been greater among females than males in the younger ages of the span in which pernicious anaemia fatalities are most common; that there has been a greater reduction in the death rate over 49 years in males than in females in Toronto since 1926.



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